PATENT SPECIFICATION (11) 1356908

1356908

(21) Application No. 10169/73 (22) Filed 2 March 1973
(31) Convention Application No. 231710 (32) Filed 3 March 1972 in
(33) United States of America (US)
(44) Complete Specification published 19 June 1974
(51) International Classification A61K 9/06
(52) Index at acceptance
A5B 241 244 245 246 247 248 24Y 26Y 351 35Y 402 40Y

(19)

(54) FATTY ALCOHOL-BUTANEDIOL-GLYCOL SOLVENT CREAM VEHICLE

ERRATA

SPECIFICATION No. 1,356,908

Page 3, line 5, *for* luryl *read* lauryl
Page 4, line 23, *for* balham *read* balsam
Page 5, line 38, *after* backbone *insert* chain

THE PATENT OFFICE
9th September, 1974

able for many drugs because their water content destroy the [illegible] medicament, in turn may destroy the emulsions, that is, break the emulsions and permit separation of the vehicle components. Furthermore, water is frequently not desirable in a medicament formulation because of its adverse effects on a condition being treated.

One system which is not subject to the above disadvantages is the non-aqueous fatty alcohol — glycol vehicle described in U.S. Patent 3,592,930 granted to Katz et al. The subject of the present invention is an improved non-aqueous cream containing a solvent system comprising butanediol and a glycol cosolvent.

Butanediols have been described as steroid solvents in solutions and lotions in U.S. Patents 3,342,676 and 3,482,018. However, these systems are free pouring liquids and do not provide the advantages of the stable cream composition of this invention.

It is accordingly the purpose of this invention to provide an essentially anhydrous water-washable base which is more effective than standard anhydrous ointment bases of the grease type because it can preserve the activity of medicaments which deteriorate in the presence of moisture; provide an occlusive film for longer and better therapeutic activity; release the medicaments more quickly and effectively; bring dissolved therapeutic agents in known dilution in contact with the skin; spread evenly and adhere well even if the skin is moist; be readily removed from the skin or fabrics with water; provide media to readily absorb discharges from wounds; serve as an excellent levigating material for many prescribed ingredients that usually require separate treatment before being incorporated into one of the bases; provide a base for medicament formulations in which water is not desired; and because it does not hydrolyze, deteriorate, become rancid, support mold growth or require preservatives.

Many medicaments which are difficult to dissolve in conventional vehicles, par-

SEE ERRATA SLIP ATTACHED

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(54) FATTY ALCOHOL-BUTANEDIOL-GLYCOL SOLVENT CREAM VEHICLE

(71) We, SYNTEX CORPORATION, a Panamanian Corporation of Apartado Postal 7386, Panama, Panama, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to vehicles for topical application of medicaments and to mixtures of the vehicle and medicaments. In particular, this invention relates to new, improved medicament vehicles having advantages over previously known vehicles.

One of the oldest types of medicament vehicles is the ointment, a preparation containing active medications that can be readily applied and rubbed into the skin. It serves as a means for distributing the medication uniformly over the skin surface and maintaining it there until beneficial action can occur. The earliest ointment preparations were based on fats, waxes, greases and petrolatum. These are, by nature, greasy, or not water-washable and have a limited ability to release medication to the skin. A non-aqueous ointment of more recent origin is a mixture of polyethylene glycols having molecular weights of 1,000 to 20,000. This vehicle, although water-washable, has a greasy texture and does not provide an occlusive dressing on a treated surface.

Emulsified creams, such as cold creams, were developed to reduce greasiness, while still maintaining the unctuousness and spreadability of the older greasy-type ointments. The emulsified creams have an aqueous base, however, and are not suitable for many drugs because their water content destroy the medicament. The medicament, in turn may destroy the emulsions, that is, break the emulsions and permit separation of the vehicle components. Furthermore, water is frequently not desirable in a medicament formulation because of its adverse effects on a condition being treated.

One system which is not subject to the above disadvantages is the non-aqueous fatty alcohol — glycol vehicle described in U.S. Patent 3,592,930 granted to Katz et al. The subject of the present invention is an improved non-aqueous cream containing a solvent system comprising butanediol and a glycol cosolvent.

Butanediols have been described as steroid solvents in solutions and lotions in U.S. Patents 3,342,676 and 3,482,018. However, these systems are free pouring liquids and do not provide the advantages of the stable cream composition of this invention.

It is accordingly the purpose of this invention to provide an essentially anhydrous water-washable base which is more effective than standard anhydrous ointment bases of the grease type because it can preserve the activity of medicaments which deteriorate in the presence of moisture; provide an occlusive film for longer and better therapeutic activity; release the medicaments more quickly and effectively; bring dissolved therapeutic agents in known dilution in contact with the skin; spread evenly and adhere well even if the skin is moist; be readily removed from the skin or fabrics with water; provide media to readily absorb discharges from wounds; serve as an excellent levigating material for many prescribed ingredients that usually require separate treatment before being incorporated into one of the bases; provide a base for medicament formulations in which water is not desired; and because it does not hydrolyze, deteriorate, become rancid, support mold growth or require preservatives.

Many medicaments which are difficult to dissolve in conventional vehicles, par-

ticularly, corticosteroids, have been found to be more soluble in butanediols. By mixing the butane-diols with other glycol cosolvents, which offer less solubility, the saturation concentration for a particular medicament can be varied to provide near saturation for a variety of concentrations of medicaments. Furthermore, the freeze-thaw stability of fatty alcohol-butanediol-glycol cosolvent combinations is surprisingly much greater than fatty alcohol-propylene glycol vehicles.

The composition of this invention is a substantially anhydrous vehicle composition consisting essentially of

(a) from 10 to 45 weight percent of saturated fatty alcohol having from 16 to 24 carbons;
(b) from 1 to 60 weight percent of 1,3-butanediol;
(c) from 10 to 85 weight percent of glycol cosolvent;
(d) from 0 to 15 weight of surfactant; and
(e) from 0 to 15 weight percent of compatible plasticizer.

The base is an improved vehicle for all types of therapeutic agents for topical application and offers particular advantages with anti-inflammatory topical steroids.

All concentrations are herein given as weight percents unless otherwise specified. It is also intended that the chemical compounds in each class of ingredients discussed hereinafter be limited to pharmaceutically acceptable, non-toxic compounds in the concentrations indicated.

The composition of this invention contains from 10 to 45 and preferably from 15 to 30 percent fatty alcohol. The fatty alcohol can be any fatty alcohol having from 16 to 24 carbons or mixtures thereof, and is preferably a saturated monohydric primary alcohol. Suitable fatty alcohols include cetyl alcohol, stearyl alcohol, behenyl alcohol, and the like.

The fatty alcohol component should be substantially free from any significant amount of unsaturated alcohols or fatty alcohols having fewer than 16 carbons, the term "substantially free from" as used herein, is defined as indicating the compositions of this invention containing less than irritating or otherwise medically undesirable amounts of the indicated substances. Since the commercially available fatty alcohols having from 16 to 24 carbon contain impurities including some proportions of fatty alcohols having fewer than 16 carbons, total avoidance of alcohols having fewer than 16 carbons from the mixture is not practicable. Careful selection of raw materials is preferable, however, to maintain the percentage of irritating alcohols to less than 10 percent of the total fatty alcohol concentration.

The composition of this invention also contains from 1 to 60 and preferably from 10 to 30 percent butanediol. The butanediol can be one or more of any of the butanediols, i.e., 1,2-butanediol, 1,3-butanediol, 1,4-butanediol or 2,3-butanediol. The preferred butanediol is 1,3-butanediol.

The composition of this invention also contains from 25 to 85 and preferably from 30 to 80 percent of glycol cosolvent. Suitable glycol cosolvents include 1,2-propanediol, 1,3-propanediol, polyethylene glycol having a molecular weight of from 100 to 800, dipropylene glycol, and the like or mixtures thereof. The glycol cosolvent is used, in combination with the butanediol to solubilize any desired amount of medicament and to maintain an optimum vehicle consistency.

The composition of this invention can contain a surfactant. The surfactant improves the consistency of the vehicle. Compositions of this invention containing surfactants tend to be thicker in consistency and more spreadable. The particular concentration will vary depending upon the choice of surfactant and the selection of the other ingredients. In general, amounts can be as low as 0.1 percent or lower. In some instances, as high as 10 percent or higher of surfactant may be desired. Generally from 2 to 5 percent is suitable. The surfactant functions as a coupling agent, linking diverse phases and maintaining a dispersion of immiscible components. Suitable surfactants include pharmaceutically acceptable, non-toxic non-ionic, anionic and cationic surfactants. Examples of suitable non-ionic surfactants include glycerol fatty acid esters such as glycerol monostearate, glycol fatty acid esters such as propylene glycol monostearate, polyhydric alcohol fatty acid esters such as sorbitan monostearate, polyethylene glycol fatty acid esters such as polyethylene glycol (400) monooleate, polyoxyethylene fatty acid esters such as polyoxyethylene (40) stearate, polyoxyethylene fatty alcohol ethers such as polyoxyethylene (20) stearyl ether, polyoxyethylene sorbitan fatty acid esters such as polyoxyethylene sorbitan monostearate, fatty acid ethanol-amides and their derivatives such as the diethanol-amide of stearic acid, and the like. Examples of suitable anionic surfactants are soaps including alkali soaps, such as sodium, potassium and ammonium salts of aliphatic carboxylic acids, usually fatty acids, such as sodium stearate. Organic amine

soaps, also included, include organic amine salts of aliphatic carboxylic acids, usually fatty acids, such as triethanolamine stearate. Another class of suitable soaps is the metallic soaps, salts of polyvalent metals and aliphatic carboxylic acids, usually fatty acids, such as aluminum stearate. Other classes of suitable anionic surfactants include sulfated fatty alcohols such as sodium luryl sulfate, sulfated oils such as the sulfuric ester of ricinoleic acid disodium salt, and sulfonated compounds such as alkyl sulfonates including sodium cetane sulfonate, amide sulfonates such as sodium N-methyl-N-oleyl taurate, sulfonated dibasic acid esters such as sodium dioctyl sulfosuccinate, alkyl aryl sulfonates such as sodium dodecylbenzene sulfonate, alkyl naphthalene sulfonates such as sodium isopropyl naphthalene sulfonate, petroleum sulfonates such as arylnaphthene with alkyl substituents. Examples of suitable cationic surfactants include amine salts such as octadecyl ammonium chloride, quaternary ammonium compounds such as benzalkonium chloride. Other examples of these and other suitable surfactants can be found in "Pharmaceutical Emulsions and Emulsifying Agents" by Lawrence M. Spatton, second edition, The Chemist and Druggist, London; "Emulsions; Theory and Practice" by Paul Becher, Reinhold Publishing Corporation, New York; and "Detergents and Emulsifiers, 1969 Annual" by John M. McCutcheon, Morristown, N.J., the disclosures thereof being incorporated herein by reference.

The composition of this invention can also contain from 0 to 15 and preferably from 0.1 to 5 percent of a compatible plasticizer. Suitable compatible plasticizers include carboxylic vinyl polymers (Carbopols — Trade Mark), polyethylene glycol having a molecular weight of from about 800 to 20,000; natural gums including acacia gum, guar gum, karaya, tragacanth, and the like; seaweed products such as agar, Irish moss and alginates; cellulose derivatives including cellulose ethers such as methyl cellulose, ethyl cellulose, sodium carboxymethyl cellulose and the like; starch, derivatives and dextrins; pectin and pectates; saponins; and water soluble or water dispersible vinyl polymers such as polyvinylpyrrolidone, polyvinyl alcohol, vinyl pyrrolidonevinyl alcohol copolymers, and the like. The plasticizer maintains homogeneity in the mixture at ambient temperatures, that is, temperatures at which the fatty alcohol is a solid. This component also improves the plasticity, and uniformity of the medicament mixtures with the vehicle and provides to the vehicle smoothness and a more pleasing "feel"; hence the vehicle containing the plasticizer is more cosmetically acceptable. In general, the particular plasticizer concentration necessary to provide a desired consistency, degree of smoothness and plasticity will vary with the choice of the fatty alcohol component and cosolvent, and the ratio of these components in the vehicle. Preferably, the plasticizer concentration should be balanced so the vehicle has freeze-thaw stability, i.e. does not separate after repeated cycles of solidification (by cooling) and liquefaction (by heating). The term "compatible" is defined herein to indicate a component which will not cause separation (loss of homogeneity) of the other components at temperatures up to 45°C.

It should be understood that the medicament vehicles of this invention can also contain other non-essential ingredients. The vehicle can contain up to 15 weight percent of conventional pharmaceutical adjuvants. These adjuvants or additives are used to improve consistency, emolliency, homogeneity, spreadability, texture and appearance of the vehicle or its residual film or the stability of the medicament. They can be used to give a residual film, varying degrees of continuity, flexibility, adhesion, occlusion, water repellency, washability, and the like. Suitable auxiliary adjuvants include hydrocarbons ranging from liquid petrolatum to solid paraffins and waxes, beeswax, saturated fatty acids having from 16 to 24 carbons such as stearic acid, palmitic acid, behenic acid; fatty acid amides such as oleamide, palmitamide, stearamide, behenamide; and esters of fatty acids having from 14 to 24 carbons such as isopropyl myristate sorbitan monostearate, polyethylene glycol monostearate, propylene glycol monostearate and the corresponding mono- and diesters of other fatty acids such as oleic acid and palmitic acid. It is preferable that the fatty acids be saturated and the fatty acids and amides be substantially free from irritating amounts of acids or amides having fewer than 14 carbons. Other optional adjuvants include miscellaneous natural products such as wool fat, wool alcohol, cholesterol and its derivatives, lecithin and proteins such as gelatin, casein, soybean protein, egg albumen. Finely dispersed mineral solids useful as thickeners include colloidal clays such as bentonite and polyvalent metal hydroxides such as maghesium hydroxide. Suitable chemical stabilizers include citric acid and other agents to adjust pH, ethylenediaminetetraacetic acid and its salts and other chelating or sequestering agents, propyl gallate, butylated hydroxy anisole or toluene, Vitamin E derivatives and other antioxidants.

The medicament vehicle of this invention is essentially a non-aqueous base, that is, it is not an aqueous emulsion and consequently is not a "cream" in the usual sense. It is preferably totally anhydrous, but can contain minor amounts of water such as up to 3 percent water. The water concentration should not be sufficient to cause separation of the other vehicle components or precipitate medicaments dissolved in the vehicle.

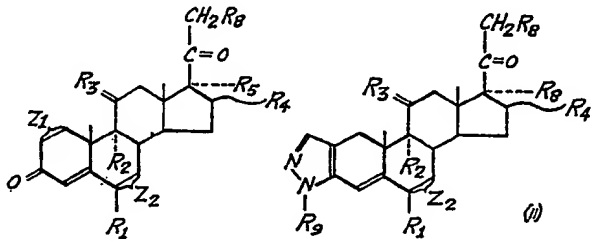
The vehicle of this invention can be made by thoroughly mixing the components at ambient or elevated temperatures. Preferably the components are thoroughly mixed while each is in a liquid state, and the mixture is cooled with good agitation to room temperature. Preferably, additional mechanical agitation and/or shock cooling steps are used as intermediate or final steps in the manufacturing process to impart more homogeneity or improved texture. Process equipment for these techniques includes heat exchangers, propeller mixers, colloid mills, homogenizers, roller mills and the like.

The base of this invention can be used as a vehicle for all types of medicaments or therapeutic agents for topical application including antibiotics such as oxytetracycline, chlortetracycline, streptomycin, bacitracin, chloramphenicol, tyrothricin and the like; steroids having anti-inflammatory or other beneficial activity; antihistamines such as prophenpyridamine maleate and diphenhydramine hydrochloride; anesthetics such as benzocaine and lidocaine; antibacterials including iodine, iodochlorohydroxyquin, nitrofurazone, sulfanilamide and derivatives, and benzalkonium chloride; fungicides such as undecylenic acid vitamins such as Vitamin A derivatives; and other therapeutic agents including coal tar, balham Peru, ammoniated mercury, anthralin, crysarobin, ichthammol, sulfur and the like.

The medicaments can be incorporated into this base by conventional techniques. A bulky, insoluble powder should be mixed before hand with a small proportion of the base mixture, 1,3-butanediol, or propylene glycol, and then blended with the remainder of the base. The products are usually improved by passing them through an ointment or roller mill. Coal tar, ichthammol, balsam Peru and others that require special processing in greasy bases can be readily incorporated in the base of this invention. The medicaments can be incorporated into the final base or introduced into the base mixture with one of its components. Heat sensitive medicaments (in particular some antibiotics) can be dissolved or suspended in a small amount of butanediol, glycol cosolvent or other liquid, and then mixed with the vehicle during or after its preparation.

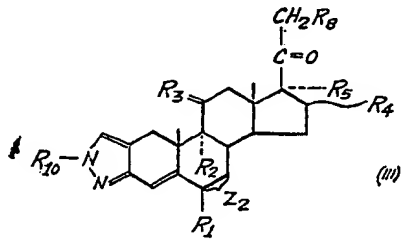
The amount of medicament to be incorporated into the base will, of course, depend upon the type of medicament and its intended use; the determination of suitable medicament concentrations is a routine matter fully within the conventional skill of the art. In general, therapeutically effective amounts of the medicament are incorporated into the vehicle.

The vehicle of this invention is particularly suitable for use with anti-inflammatory topical steroids represents by Formulas I, II and III.



(I)

(II)



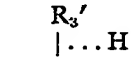
(III)

In the above formulas

R_1 is hydrogen, methyl, fluoro, or chloro and when Z_2 is a single bond, R_1 can be either α or β oriented;

R_2 is hydrogen, chloro, or fluoro;

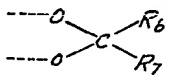
R_3 is keto or



wherein R_3' is hydrogen, hydroxy, chloro, or fluoro;

R_4 is hydrogen, methyl, hydroxy, or a conventional hydrolyzable ester thereof;

R_5 is hydrogen, hydroxy, a conventional hydrolyzable ester thereof, or when taken together with R_4;



wherein

R_6 is hydrogen or alkyl of up to eight carbons, and

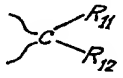
R_7 is hydrogen, or alkyl or an aryl group of up to eight carbons;

R_8 is hydroxy, conventional hydrolyzable esters thereof, tetrahydropyranyloxy, tetrahydrofuranyloxy, 4'-(lower)alkoxytetrahydropyran-4'-yloxy, lower alkoxy, lower cycloalkoxy, lower cycloalkenyloxy, chloro, or fluoro;

R_9 and R_{10} are hydrogen, methyl, phenyl, chlorophenyl, fluorophenyl, methylphenyl, or methoxyphenyl (the substituted phenyls preferably being substituted in the para position);

R_{11} and R_{12} each is hydrogen, chloro or fluoro;

Z_1 and Z_2 each is a single bond, double bond, or



The terms "(lower)alkyl" and derivations thereof appearing in the above definitions and elsewhere in the instant specification denote alkyl groups having from one to six carbon atoms, inclusive, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, amyl, hexyl and the like.

The term "conventional hydrolyzable ester" as used herein denotes those hydrolyzable ester groups conventionally employed in the steroid art, preferably those derived from hydrocarbon carboxylic acids or phosphoric acids and their salts. The term "hydrocarbon carboxylic acid" defines both substituted and unsubstituted hydrocarbon carboxylic acids. These acids can be completely saturated or possess varying degrees of unsaturation (including aromatic), can be of straight chain, branched chain, or cyclic structure, and preferably contain from one to 12 carbon atoms. In addition, they can be substituted by functional groups, for example, hydroxy, alkoxy containing up to six carbon atoms, acyloxy containing up to 12 carbon atoms, nitro, amino, halogeno, and the like, attached to the hydrocarbon backbone. Typical conventional hydrolyzable esters thus included within the scope of the term and the instant invention are acetate, propionate, butyrate, valerate, caproate, enanthate, caprylate, pelargonate, acrylate, undecenoate, phenoxyacetate, benzoate, phenylacetate, diphenylacetate, diethylacetate, trimethylacetate, t-butylacetate, trimethylhexanoate, methylneopentylacetate, cyclohexylacetate, cyclopentylpropionate, adamantoate, glycolate, methoxyacetate, hemisuccinate, hemiadipate, hemi-β,β-dimethylglutarate, acetoxyacetate, 2-chloro-4-nitrobenzoate, aminoacetate, diethylaminoacetate, piperidinoacetate, β-chloropropionate, trichloroacetate, β-chlorobutyrate, nicotinate, isonicotinate, benzofuran-2-carboxylate, 1-methoxyacetate, dihydrogen phosphate, dibenzyl phosphate, benzyl hydrogen phosphate, sodium benzyl phosphate, cyclohexylammonium benzyl phosphate, sodium phenyl phosphate, sodium ethyl phosphate, di-p-nitrobenzyl phosphate, sodium o-methoxyphenyl phosphate, cyclohexylammonium p-cyanobenzyl phosphate, sodium phenacyl phosphate, benzyl o-carbomethoxyphenyl phosphate, and the like.

By the term "aryl" are included aryl, aralkyl, and alkaryl groups, such as phenyl,

p-chlorophenyl, p-methoxyphenyl, benzyl, phenethyl, tolyl, ethylphenyl, and the like. The wavy line (~) designates and includes both the alpha and beta configurations.

The above anti-inflammatory steroids have been previously disclosed in United States Patents 3,365,446; 3,067,194; 3,364,203; 3,053,838; and 3,513,162 for example.

The above anti-inflammatory topical medicaments are thoroughly mixed with the base in therapeutically effective amounts. The particular concentration of the medicament in the base will vary depending upon the particular activity of the steroid used considered in conjunction with the condition and subject to be treated. In general, therapeutically effective amounts of these compounds can be as low as 0.00001 weight percent or lower, for example. For some uses, as high as 5 weight percent steroid or higher may be desired.

The medicament base of this invention has been found to be particularly suitable for use with topical corticoids, for example, 6α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-21-acetoxypregna-1,4-diene-3,20-dione, fluocinolone acetonide (6α, 9α - difluoro - 11β,21 - dihydroxy - 16α,17α - isopropylidenedioxypregna - 1,4-diene - 3,20 - dione), fluocinolide (21 - acetoxy - 6α,9α - difluoro - 11β - hydroxy-16α,17α - isopropylidenedioxypregna - 1,4 - diene - 3,20 - dione), 9α,11β - dichloro - 6α - fluoro - 21 - hydroxy - 16α,17α - isopropylidenedioxypregna - 1,4-diene - 3,20 - dione, 9α,11β - dichloro - 6α,21 - difluoro - 16α,17α - isopropylidenedioxypregna - 1,4 - diene - 3,20 - dione and 9α,11β,21 - trichloro - 6α - fluoro-16α,17α - isopropylidenedioxypregna - 1,4 - diene - 3,20 - dione.

This invention is further illustrated by the following specific but non-limiting examples.

EXAMPLE 1

The following ingredients are mixed at 80°C and cooled to room temperature with good agitation.

	Concentration, Wt. Percent				
Ingredients	A	B	C	D	E
1,3-Butanediol	16.0	24.0	15.0	40.0	20.0
Polyoxyethylene (20) sorbitan monostearate (Tween 60)	1.8	1.8	—	—	—
Sorbitan monostearate	2.2	2.2	0.5	2.2	—
Stearyl alcohol	16.0	20.0	25.0	30.0	30.0
Carboxy vinyl polymer (Carbopol 940)	—	—	0.3	0.5	0.5
Polyethylene glycol (molecular wt. 6000)	—	—	—	—	5.0
Propylene glycol	64.0	52.0	59.2	27.3	44.5

Carbopol and Tween are registered Trade Marks.

EXAMPLE 2

A vehicle having the composition "C" of Example 1 and containing 0.025 g. of 9α,11β,21 - trichloro - 6α - fluoro - 16α,17α - isopropylidenedioxypregna - 1,4-diene - 3,20 - dione is prepared as follows. The 1,3-butanediol and propylene glycol are heated together at 85°C, and the steroid is dissolved in the mixture with stirring. The carboxy vinyl polymer is mixed with the stearyl alcohol and the resultant mixture is mixed with the solution containing the steroid. The sorbitan monostearate is added to the mixture, and the mixture is stirred until homogeneous and cooled to room temperature with proper agitation.

EXAMPLE 3

Each of 0.25, 0.5 and 1.0 gm, quantities of the following anti-inflammatory steroids, when incorporated into 1000 gm. the mixtures described in Example 1, are effective for topical treatment of inflammation:

9α,11β-dichloro-6α-fluoro-21-hydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione,

9α-fluoro-11β,17α,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione,

9α-fluoro-11β,21-dihydroxy-16β-methyl-17α-valeroxypregna-1,4-diene-3,20-dione,

17α,21-dihydroxypregn-4-ene-3,11,20-trione,

21-acetoxy-17α-hydroxypregn-4-ene-3,11,20-trione,
21-hydroxypregn-4-ene-3,20-dione,
21-acetoxypregn-4-ene-3,20-dione,
21-pivaloxypregn-4-ene-3,20-dione,
9α-fluoro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione,
9α-fluoro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione-21-sodium phosphate,
6α,9α-difluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione,
6α,9α-difluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-21-acetoxypregna-1,4-diene-3,20-dione,
9α-fluoro-11β,17α-dihydroxy-6α-methylpregna-1,4-diene-3,20-dione,
6α-fluoro-11β,17α,21-trihydroxypregna-1,4-diene-3,20-dione,
6α-fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxypregn-4-ene-3,20-dione,
6α-fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione,
21-acetoxy-11β,17α-dihydroxypregn-4-ene-3,20-dione,
11β,17α,21-trihydroxy-6α-methylpregna-1,4-diene-3,20-dione,
6α-methyl-11β,17α-dihydroxy-21-acetoxypregna-1,4-diene-3,20-dione,
6α-fluoro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione,
21-acetoxy-6α-fluoro-11β,17α-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione,
6α-fluoro-11β,17α-dihydroxy-16α-methyl-21-valeroxypregna-1,4-diene-3,20-dione,
6α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-21-acetoxy-pregna-1,4-diene-3,20-dione,
11β,17α,21-trihydroxypregna-1,4-diene-3,20-dione,
21-acetoxy-11β,17α-dihydroxypregna-1,4-diene-3,20-dione,
17α,21-dihydroxypregna-1,4-diene-3,11,20-trione,
21-acetoxy-17α-hydroxypregna-1,4-diene-3,11,20-trione,
9α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione,
21-acetoxy-9α-fluoro-11β,16α,17α-trihydroxypregna-1,4-diene-3,20-dione,
9α-fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxy-pregna-1,4-diene-3,20-dione,
6α-fluoro-9α,11β-dichloro-21-hydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione,
6α,9α-difluoro-11β,21-dihydroxy-16α-methyl-17α-valeroxypregna-1,4-diene-3,20-dione,
6α,9α-difluoro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione,
6α,7α-difluoromethylene-11β,17α,21-trihydroxypregna-4-ene-3,20-dione,
6α-fluoro-11β,21-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione,
21-chloro-6α,9α-difluoro-11β-hydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione,
9α,11β-dichloro-6α,21-difluoro-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione, and
9α,11β,21-trichloro-6α-fluoro-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione.

EXAMPLE 4

Repeating the procedure of Example 1 with

(a) from 10 to 45 percent of a fatty alcohol having from 16 to 24 carbons, e.g., cetyl alcohol, stearyl alcohol, behenyl alcohol, etc.;
(b) from 1 to 60 percent of one or more of the butanediols;
(c) from 10 to 85 percent glycol cosolvent such as 1,2-propanediol, 1,3-propanediol, polyethylene glycol (M.W. 100 to 800), dipropylene glycol, etc.;
(d) from 0 to 15 percent of a surfactant such as sorbitan monooleate; and
(e) from 0 to 15 percent compatible plasticizer, e.g., carboxy vinyl polymer (Carbopol)

yields an improved medicament base according to this invention.

EXAMPLE 5

Repeating the procedure of Example 2 with the ingredients of Example 3 yields improved compositions for topical treatment of inflammation according to this invention.

WHAT WE CLAIM IS:—

1. A substantially anhydrous vehicle composition consisting essentially of
(a) from 10 to 45 weight percent of saturated fatty alcohol having from 16 to 24 carbons;
(b) from 1 to 60 weight percent of butanediol;
(c) from 10 to 85 weight percent of glycol cosolvent;
(d) from 0 to 15 weight percent of surfactant; and
(e) from 0 to 15 weight percent of compatible plasticizer.

2. The composition of Claim 1 comprising
(a) from 15 to 30 weight percent of saturated fatty alcohol having from 16 to 24 carbons;
(b) from 10 to 30 weight percent of butanediol;
(c) from 30 to 80 weight percent of glycol cosolvent;
(d) from 0.1 to 10 weight percent surfactant; and
(e) from 0 to 15 weight percent of compatible plasticizer.

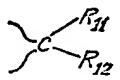
3. The composition of Claim 2 wherein the butanediol is 1,3-butanediol.

4. The composition of Claim 2 wherein the compatible plasticizer concentration is from 0.1 to 5 weight percent.

5. A mixture of the vehicle composition of Claim 1 with a topically active medicament.

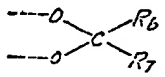
6. The composition of Claim 5 wherein the medicament is an anti-inflammatory steroid.

7. The composition of Claim 6 wherein the steroid is
(a) a pregn-4-ene-3,20-dione having at each of positions C-1,2 and C-6,7, a single bond, double bond or the group having the formula

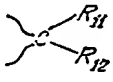


wherein R_{11} and R_{12} each is hydrogen, chloro or fluoro; at position C-6, hydrogen, methyl, fluoro or chloro; at position C-9, hydrogen, chloro, or fluoro; at position C-11, keto or

wherein R_3' is hydrogen, hydroxy, chloro or fluoro; at position C-16, hydrogen, methyl, hydroxy or conventional hydrolyzable esters thereof; at position C-17α, hydrogen, hydroxy, conventional hydrolyzable esters thereof, or when taken together with C-16α, a group having the formula



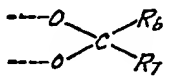
wherein R_6 is hydrogen or alkyl of up to 8 carbons, and R_7 is hydrogen, or alkyl or aryl having up to 8 carbons; and at position C-21, hydroxy, conventional hydrolyzable esters thereof, tetrahydropyranyloxy, tetrahydrofuranyloxy, (lower)alkoxytetrahydropyran-4'-yloxy, lower alkoxy, lower cycloalkoxy, lower cycloalkenyloxy, chloro or fluoro;
(b) a 2' - substituted - pregn - 4 - ene - 20 - one - [3,2 - c] - pyrazole or a 1' - substituted - pregn - 4 - en - 20 - one - [3,2 - c] - pyrazole having at the respective N-2' or N-1' positions, hydrogen, methyl, phenyl, chlorophenyl, fluorophenyl, methylphenyl, or methoxyphenyl, and having at C-6,7, a single bond, double bond or group having the formula



wherein R_{11} and R_{12} each is hydrogen, chloro or fluoro; at position C-6,

hydrogen, methyl, fluoro or chloro; at position C-9, hydrogen, chloro, or fluoro; at position C-11, keto or

wherein R_3' is hydrogen, hydroxy, chloro or fluoro; at position C-16, hydrogen, methyl, hydroxy or conventional hydrolyzable esters thereof, at position C-17α, hydrogen, hydroxy, conventional hydrolyzable esters thereof, or when taken together with C-16α, a group having the formula



wherein R_6 is hydrogen or alkyl of up to 8 carbons, and R_7 is hydrogen, or alkyl or aryl having up to 8 carbons; and at position C-21, hydroxy, conventional hydrolyzable esters thereof, tetrahydropyranyloxy, tetrahydrofuranyloxy, 4'-(lower)alkoxytetrahydropyran-4'-yloxy, lower alkoxy, lower cycloalkoxy, lower cycloalkenyloxy, chloro or fluoro.

8. The composition of Claim 7 wherein the steroid is 9α,11β,21-trichloro-6α-fluoro-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione.

9. The composition of Claim 8 consisting essentially of the steroid and

(a) from 15 to 30 weight percent of saturated fatty alcohol having from 16 to 24 carbons;

(b) from 10 to 30 weight percent of 1,3-butanediol;

(c) from 30 to 80 weight percent of glycol cosolvent, the weight ratio of glycol solvent to propylene carbonate being at least 1:1;

(d) from 0.1 to 10 weight percent surfactant, and

(e) from 0 to 15 weight percent of compatible plasticizer.

10. The composition of Claim 9 wherein the compatible plasticizer concentration is from 0.1 to 5 weight percent.

11. The composition of Claim 7 wherein the steroid is 21-acetoxy-6α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-pregna-1,4-diene-3,20-dione.

12. A composition according to claim 1 substantially as herein described or exemplified.

13. A medicated composition according to claim 5 substantially as herein described or exemplified.

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Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1974.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.